

What is claimed is:

1. A method for treating a serious psychotic mental illness comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of a combination of (i) an  $\alpha_2$  -adrenergic receptor antagonist and (ii) an atypical antipsychotic neuroleptic which has a greater antagonist affinity for D<sub>2</sub> dopamine receptor than its antagonist affinity for  $\alpha_2$  adrenergic receptor in a pharmaceutically acceptable carrier.
2. A method as claimed in claim 1, wherein said  $\alpha_2$ -adrenergic receptor antagonist (i) is selected from the group consisting of idazoxan, yohimbine, ethoxy-idazoxan, fluperoxan and atipamezole.
3. A method as claimed in claim 2 wherein said  $\alpha_2$ -adrenergic receptor antagonist (i) is idazoxan.
4. A method as claimed in claim 1, wherein said antipsychotic neuroleptic drug is selected from the group consisting of olanzapine, risperidone, quetiapine, ziprasidone, sertindole and aripiprazole.
5. A method as claimed in claim 1, wherein said  $\alpha_2$ -adrenergic receptor antagonist (i) is administered in an amount from about 60 to 120 mg/day.
6. A method as claimed in claim 1, wherein said serious psychotic mental illness is schizophrenia.
7. A pharmaceutical composition comprising a combination of (i) an  $\alpha_2$ -adrenergic receptor antagonist, (ii) an atypical antipsychotic neuroleptic which has a greater antagonist affinity for D<sub>2</sub> dopamine receptor than its antagonist affinity for  $\alpha_2$  adrenergic receptor, and (iii) a pharmaceutically acceptable carrier, wherein the amount of said ingredients (i) and (ii) is therapeutically effective against serious psychotic mental illness.
8. A composition as claimed in claim 7, wherein said  $\alpha_2$ -adrenergic receptor antagonist (i) is selected from the group consisting of idazoxan, yohimbine, ethoxy-idazoxan, fluperoxan and atipamezole.
9. A composition as claimed in claim 8, wherein said  $\alpha_2$ -adrenergic receptor antagonist (i) is idazoxan.

10. A composition as claimed in claim 7, wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, risperidone, quetiapine, ziprasidone, sertindole and aripiprazole.

11. A method for treating a serious psychotic mental illness comprising the step of  
5 administering to a patient in need of such treatment a therapeutically effective amount of a combination of (i) an  $\alpha_2$ -adrenergic receptor antagonist and (ii) an atypical antipsychotic in a pharmaceutically acceptable carrier, wherein said serious psychotic mental illness is selected from the group consisting of Schizophreniform Disorder, Severe Schizoaffective Disorder with Psychotic Features, Bipolar I Disorders with a  
10 Single Manic Episode, Severe Bipolar I Disorders with Psychotic Features, Major Depressive Disorders Manifesting a Single Episode, Severe Major Depressive Disorders with Psychotic Features, Bipolar I Disorders Manifesting a Mixed Most Recent Episode, Severe Bipolar I Disorders with Psychotic Features, Brief Psychotic Disorders, Psychotic Disorders NOS, Paranoid Personality Disorders, Schizoid  
15 Personality Disorders, Schizotypal Personality Disorders with Sedative, Hypnotic, or Anxiolytic Manifestations, Major Depressive Disorders with Recurrent Episodes, and Psychotic Disorders due to Specific General Medical Conditions.

12. The method as claimed in claim 11, where to said  $\alpha_2$ -adrenergic receptor antagonist (i) is one or more selected from the group consisting of idazoxan,  
20 yohimbine, ethoxy-idazoxan, fluperoxan and atipamezole.

13. The method as claimed in claim 11, wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, risperidone, quetiapine, ziprasidone, sertindole and aripiprazole.

14. The method as claimed in claim 11, wherein said  $\alpha_2$ -adrenergic receptor  
25 antagonist (i) is administered in an amount from about 60 to 120 mg/day.

15. A method for treating a serious psychotic mental illness comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of a combination of (i) a compound having combined  $D_2$  dopamine and  $5HT_2$  serotonin antagonist activities, wherein said compound (ii) has a greater antagonist  
30 affinity for  $D_2$  dopamine receptor than its antagonist affinity for  $\alpha_2$  adrenergic receptor and (ii) a compound having  $\alpha_2$  adrenergic receptor antagonist activity.

16. The method of claim 15 wherein said D<sub>2</sub> dopamine and 5HT<sub>2</sub> serotonin antagonist is an atypical antipsychotic drug.

17. The method of claim 16 wherein said atypical antipsychotic is selected from the group consisting of olanzapine, risperidone, quetiapine, ziprasidone, sertindole  
5 and aripiprazole.

18. The method of claim 15 wherein said  $\alpha_2$ -adrenergic receptor antagonist is selected from the group consisting of idazoxan, yohimbine, ethoxy-idazoxan, fluperoxan and atipamezole.

19. The method of claim 18 wherein said  $\alpha_2$ -adrenergic receptor antagonist is  
10 idazoxan.

20. The method of claim 15 wherein said D<sub>2</sub> dopamine and 5HT<sub>2</sub> serotonin antagonist is olanzapine.

21. A method for treating a serious psychotic mental illness comprising the step of administering to a patient in need of such treatment a therapeutically effective  
15 amount of a combination of idazoxan and olanzapine.

22. The method of claim 15 wherein the amount of said D<sub>2</sub> dopamine and 5HT<sub>2</sub> serotonin antagonist administered to said patient is reduced to approximately 50% of the normally recommended dose.

23. The method of claim 15 wherein said D<sub>2</sub> dopamine and 5HT<sub>2</sub> serotonin  
20 antagonist comprises an in vivo D<sub>2</sub> occupancy of approximately 50%.

24. The method of claim 15 wherein the serious psychotic disorder is chosen from the group consisting of schizophreniform disorder, severe schizoaffective disorder with psychotic features, bipolar I disorders with a single manic episode, severe bipolar I disorders with psychotic features, major depressive disorders  
25 manifesting a single episode, severe major depressive disorders with psychotic features, bipolar I disorders manifesting a mixed most recent episode, severe bipolar I disorders with psychotic features, brief psychotic disorders, psychotic disorders NOS, paranoid personality disorders, schizoid personality disorders, schizotypal personality disorders, major depressive disorders with recurring episodes, and psychotic disorders  
30 due to specific general medical conditions.

25. The method of claim 15 wherein said serious psychotic mental illness is schizophrenia.

26. A method for treating a serious psychotic mental illness in a patient in need thereof which comprises co-administration of (i) a compound having combined D<sub>2</sub> dopamine and 5HT<sub>2</sub> serotonin antagonist activities, wherein said compound has a greater antagonist affinity for D<sub>2</sub> dopamine receptor than its antagonist affinity for  $\alpha_2$  adrenergic receptor, and (ii) a compound having  $\alpha_2$  adrenergic receptor antagonist activity, wherein said compound (i) is administered initially alone in an amount and for a period of time sufficient to stabilize said patient and subsequently said compound (ii) is co-administered in an amount and for a period of time that allows for a reduction in the amount of compound (i) administered to said patient.

27. The method of claim 26 further comprising the step of reducing the amount of compound (i) administered to said patient after commencing co-administration of compound (ii).

28. The method of claim 27 wherein the dose of said compound (i) administered to the patient is reduced to approximately 50% of the dose administered to stabilize said patient.

29. The method of claim 26 wherein the serious psychotic disorder is chosen from the group consisting of schizophreniform disorder, severe schizoaffective disorder with psychotic features, bipolar I disorders with a single manic episode, severe bipolar I disorders with psychotic features, major depressive disorders manifesting a single episode, severe major depressive disorders with psychotic features, bipolar I disorders manifesting a mixed most recent episode, severe bipolar I disorders with psychotic features, brief psychotic disorders, psychotic disorders NOS, paranoid personality disorders, schizoid personality disorders, schizotypal personality disorders, major depressive disorders with recurring episodes, and psychotic disorders due to specific general medical conditions.

30. The method of claim 26 wherein said serious psychotic mental illness is schizophrenia.

31. A method for treating a serious psychotic mental illness comprising the step of administered to a patient in need of such treatment a therapeutically effective

amount of a combination of (i) a compound that blocks or down-regulates D<sub>2</sub> dopamine and 5HT<sub>2</sub> serotonin receptor activities and (ii) a compound that blocks or down-regulates  $\alpha_2$  adrenergic receptor activity.

32. The method of claim 31 wherein said compound (ii) is a norepinephrine reuptake inhibitor.

33. The method of claim 31 wherein said compound (ii) is a selective serotonin reuptake inhibitor.

34. The method of claim 31 wherein said compound (ii) is an anti-sense RNA molecule.

35. A method for treating a serious psychotic disorder in a patient in need thereof which comprises administering an atypical antipsychotic in combination with an effective amount of an  $\alpha_2$  antagonist to provide antipsychotic effects at D<sub>2</sub> receptor occupancy levels of less than or equal to 60%.

36. The method of claim 35 wherein the D<sub>2</sub> occupancy levels are less than or equal to 50%.

37. The method of claim 36 wherein D<sub>2</sub> occupancy levels are measured by positive emission tomography (PET) or single photon emission computerized tomography (SPECT).

38. The method of claim 35 wherein the  $\alpha_2$  antagonist is selected from the group consisting of idazoxan, yohimbine, ethoxy-idazoxan, fluperoxan, and atipamezole.

39. The method of claim of 35 wherein the atypical D<sub>2</sub> antagonist is selected from the group consisting of olanzapine, quetiapine, risperidone, sertindole and ziprasidone.

40. The method of claim 35 wherein the atypical antipsychotic and the  $\alpha_2$  antagonist are administered separately.

41. The method of claim 35 wherein the atypical antipsychotic and the  $\alpha_2$  antagonist are administered in combination.

42. The method of claim 41 wherein the atypical antipsychotic and the  $\alpha_2$  antagonist are in different compositions.

43. The method of claim 41 wherein the atypical antipsychotic and the  $\alpha_2$  antagonist are in the same composition.

44. The method of claim 35 wherein one or both of the atypical antipsychotic and the  $\alpha_2$  antagonist comprise a mixture of enantiomers of said compounds.

45. The method of claim 44 wherein the atypical D<sub>2</sub> antagonist mixture comprises from 95/5 to 5/95 mole ratios of the enantiomers of the particular atypical antipsychotic compound.

46. The method of claim 44 wherein the  $\alpha_2$  antagonist mixture comprises from 95/5 to 5/95 mole ratios of the enantiomers of the particular  $\alpha_2$  antagonist compound.

47. The method of claim 35 wherein one or both of the atypical antipsychotic and the  $\alpha_2$  antagonist is administered substantially in the form of a single enantiomer.

48. The method of claim 47 wherein the  $\alpha_2$  antagonist is administered substantially in the form of a single enantiomer

49. The method of claim 48 wherein the (+) enantiomer of idazoxan is administered.

50. The method of claim 35 wherein the serious psychotic disorder is chosen from the group consisting of schizophreniform disorder, severe schizoaffective disorder with psychotic features, bipolar I disorders with a single manic episode, severe bipolar I disorders with psychotic features, major depressive disorders manifesting a single episode, severe major depressive disorders with psychotic features, bipolar I disorders manifesting a mixed most recent episode, severe bipolar I disorders with psychotic features, brief psychotic disorders, psychotic disorders NOS, paranoid personality disorders, schizoid personality disorders, schizotypal personality disorders, major depressive disorders with recurring episodes, and psychotic disorders due to specific general medical conditions.

51. The method of claim 35 wherein the serious psychotic disorder is child or early adolescent schizophrenia.

52. The method of claim 51 wherein patient in need of treatment is from about age 9 years to 15 years.

53. The method of claim 51 wherein the serious psychotic disorder is childhood onset schizophrenia.

54. A method for treating a serious psychotic disorder in a patient in need thereof which comprises administering an atypical antipsychotic in combination with an

effective amount of a compound which enhances noradrenergic synaptic activity to provide antipsychotic effects at D<sub>2</sub> receptor occupancy levels of less than or equal to 60%.

5 55. The method of claim 54 wherein the D<sub>2</sub> occupancy levels are less than or equal to 50%.

56. The method of claim 54 wherein D<sub>2</sub> occupancy levels are measured by positive emission tomography (PET) or single photon emission computerized tomography (SPECT).

10 57. The method of claim 54 wherein the compound which enhances noradrenergic synaptic activity chosen from the group consisting of reboxetine, atomoxetine, or a compound that inhibits the norepinephrine transporter.

58. The method of claim of 54 wherein the atypical D<sub>2</sub> antagonist is selected from the group consisting of olanzapine, quetiapine, risperidone, sertindole and ziprasidone.

15 59. The method of claim 54 wherein the serious psychotic disorder is chosen from the group consisting of schizophreniform disorder, severe schizoaffective disorder with psychotic features, bipolar I disorders with a single manic episode, severe bipolar I disorders with psychotic features, major depressive disorders manifesting a single episode, severe major depressive disorders with psychotic features, bipolar I disorders manifesting a mixed most recent episode, severe bipolar I disorders with psychotic features, brief psychotic disorders, psychotic disorders NOS, paranoid personality disorders, schizoid personality disorders, schizotypal personality disorders, major depressive disorders with recurring episodes, and psychotic disorders due to specific general medical conditions.

25 60. The method of claim 54 wherein the serious psychotic disorder is child or early adolescent schizophrenia.

61. The method of claim 60 wherein patient in need of treatment is from about age 9 years to 15 years.

30 62. The method of claim 60 wherein the serious psychotic disorder is childhood onset schizophrenia.

63. A method of treating a serious psychotic disorder involving the administration of at least one atypical antipsychotic and at least one  $\alpha_2$  adrenergic receptor antagonist wherein the improvement comprises selecting atypical antipsychotics and  $\alpha_2$  receptor antagonists such that the receptor affinity ratios for  $D_2/\alpha_2$  ranges from about .8 to about 4.5.

64. The method of claim 63 wherein the ratio of  $D_2/\alpha_2$  ranges from about .85 to about 3.9.

65. The method of claim 63 wherein the ratio of  $D_2/\alpha_2$  from about .95 to about 1.05.

66. The method of claim 63 wherein the ratio of  $D_2/\alpha_2$  ranges from about .95 to 1.00.

67. The method of claim 63 wherein the ratio of  $D_2/\alpha_2$  is about 1.0.

68. A method for treating a serious psychotic illness comprising administering at least one atypical antipsychotic and at least one  $\alpha_2$  adrenergic receptor antagonist wherein the dosage balance between the atypical antipsychotic and  $\alpha_2$  antagonist is equivalent to a ratio of 900-1100 mg equivalents of chlorpromazine and an amount of an  $\alpha_2$  antagonist that provides for about equal  $D_2/\alpha_2$  receptor saturation.

69. The method of claim 68 wherein the amount of  $D_2$  antagonist is equivalent to about 950-1050 mg equivalents of chlorpromazine.

70. The method of claim 68 wherein the  $\alpha_2$  antagonist is selected from the group consisting of idazoxan, yohimbine, ethoxyidazoxan, fluperoxan, and atipamezole.

71. The method of claim 68 wherein the atypical  $D_2$  antagonist is selected from olanzapine, quetiapine, risperidone, sertindole and ziprasidone.

72. A method for identifying compounds that are useful to treat serious psychotic mental illness which comprises subjecting a candidate compound to an assay demonstrating affinity for the  $D_2$  dopamine receptor and an assay demonstrating affinity for the  $\alpha_2$  adrenergic receptor and determining that the compound demonstrates significant affinity for both the  $D_2$  dopamine receptor and the  $\alpha_2$  adrenergic receptor.



73. The method of claim 72, further comprising the step of determining that the candidate compound comprises between about 2 to about 15 fold greater affinity for the  $\alpha_2$  adrenergic receptor than for D<sub>2</sub> receptor.

74. The method of claim 72 further comprising the step of subjecting the candidate compound to an assay demonstrating affinity to 5HT<sub>2</sub> serotonin receptors and determining that the compound does not demonstrate significant affinity for the 5HT<sub>2</sub> serotonin receptors.

75. A method for treating a serious psychotic mental illness comprising the step of administered to a patient in need of such treatment a therapeutically effective amount of a compound identified by the methods of any of claims 72-74.

76. A pharmaceutical composition for treating a serious psychotic mental illness comprising a therapeutically effective amount of a compound identified by the methods of any of claims 72-74 and a pharmaceutically acceptable carrier.

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